Doctoral Theses (Summaries)

Drugs and Breast-feeding – Epidemiological and Pharmacokinetic Studies on Drugs and Breast-feeding

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As early as 1500 B.C. the fact that drugs enter breast milk was probably recognized. The first review about drugs excreted in breast milk was written in 1907 by Bucura who emphasized the importance to determine whether the administration of medicines to the mother could injure her child; conversely one could also exploit therapeutically this passage of medicines into the milk.

The belief that drugs given to the mother exert their effect on the breast-fed child has been strong, although based on many anecdotal and spurious case reports. Old data of dubious value have sometimes been quoted and requoted long after they should have been discredited; as a result risks have sometimes been underestimated, quite often overestimated.

When the present work started drugs were still categorized in those which are and those which are not excreted in breast milk, resulting in inappropriate advices to mothers about not breast-feeding when using the former drugs.

Aims. The overall *aim* of this study was to survey and critically analyse drug use by the mother and her breast-fed infant, passive as well as active exposure, at various stages during lactation (in the maternity ward and the community) and to quantify the amount of some selected drugs and diagnostics in human breast milk. The impact of breast-feeding and other determinants on the use of drugs and some sociostimulants, such as coffee, cigarettes and alcohol was also included in the studies.

Results and Implications. The present studies indicate that drugs frequently prescribed to 970 women in maternity wards of five university hospitals lacked documentation about the amount excreted in breast milk, although the prevalence of breast-feeding at one week after birth was 97% (paper I, II). Furthermore, the proportion of women who used hypnotics, analgesics, uterine contracting agents and antiinfectives varied considerably between hospitals, probably due to established therapeutic traditions and lack of therapeutic guidelines.

Drug Use. A correlation between maternal and infant (n = 885) drug use in the community was found, which suggests a complex interaction of medicosocial variables between mother and child (III, IV). Most (85%) of the drugs given to infants was claimed to be recommended by health personnel. Frequently re-

ceived drugs were for minor disorders. The passive amount of drug received through breast milk, comprised 1/7 of the total average drug exposure calculated in breast-fed infants. No difference between drug exposure in breast-fed and non-breast-fed (weaned) infants was found.

50% of the mothers claimed they had similar or more doubts about drug use during lactation than during pregnancy. However, infant exposure to drugs in breast milk was in fact exceeded by exposure to nicotine in terms of proportions of daily users.

Smoking. The frequency of breast-feeding at 3 months was considerably higher in non-smoking than in smoking mothers. Smoking mothers seemed more often to have an insufficient milk production. A higher frequency of infantile colic was reported by mothers who breast-fed and smoked than in those who breast-fed and did not smoke. A preference for the female gender was also observed as girls had a higher prevalence of breast-feeding than boys. In the present study breast-feeding was associated with a lower frequency of gastro- intestinal disorders, but confounding factors may play an important role.

Milk Transfer. In spite of its poor documentation in breast-feeding mothers, nitrazepam was the most frequently prescribed drug in the maternity wards (paper II). A pharmacokinetic and clinical study (paper V) of repeated doses of nitrazepam and midazolam in the immediate postpartum period showed that nitrazepam, but not midazolam accumulated in breast milk. However, the amount excreted was to small to be expected to have a pharmacological effect. Midazolam had the least quantity in breast milk, but slightly less hypnotic effect than nitrazepam. The relatively large interindividual variation in milk-plasma ratio of lipid-soluble nitrazepam (at 7 hours) and zopiclone was not explained by plasma protein correlates or days since delivery (stage of lactation). Mode of delivery did not seem to influence the milk transfer.

A hypothesis about higher milk transfer and infant exposure of penicillin during mastitis was not supported. Increased rate of penicillin milk transfer was demonstrated by a higher peak concentration and a tendency to shorter time to peak seen in inflamed versus control breasts. No differences between mastitic, non-mastitic and control breast milk in area under the milk curve were observed after one dose of phenoxymethyl- penicillin (paper VII). A leakage of extracellular fluid to breast milk during mastitis was demonstrated.

Iodine-containing contrast media has not been warranted in lactating women (or required a transient stop in breast-feeding). The present studies showed a minimal excretion of metrizamide and iohexol in breast milk after radiological procedures (paper VIII). The water-solubility and the high molecular weight of these non-protein bound agents may probably explain the slow and limited passage from plasma to breast milk.

Leakage of drugs through the paracellular pathway between alveolar cells allowing components of extracellular fluid to enter milk spaces was supported by the finding of the high iohexol concentrations in milk from a weaning mother (paper VIII) as well as the findings of elevated sodium and albumin accompanying the higher rate of penicillin transfer in inflamed breasts as compared to control breasts (paper VII).

Infant Dose. The estimated amount of single doses of nitrazepam, midazolam and zopiclone found in early breast milk was on average 3.6%, < 0.2%, and 1.4% of the weight-related dose to the mother, assuming that daily milk intake is 150 ml/kg for a baby less than 6 months.

The relative dose to the infant of short courses of nitrazepam, midazolam, zopiclone and phenoxy-methylpenicillin and single doses of iohexol and metrizoate received from breast milk was very low and would in general, and in particular if weighed against the beneficial effect of breast milk, *justify* breast-feeding during maternal treatment.

This dissertation is based on the following papers:

I. Matheson I. Medikamentrutiner ved norske barselavdelinger. Tidssk Nor Lægeforen 1985; 105: 2281-4.
II. Matheson I. Medikamenter til mor og barn i barselavdeling. En kartlegging ved fem norske universitetssykehus. Tidsskr Nor Lægeforen 1989; 109: 2118-22.
III. Matheson I, Kristensen K, Lunde PKM. Spedbarns plager og legemiddelbruk. Hvilken betydning har amming? Tidsskr Nor Lægeforen 1989; 109: 2123-8. IM0305.93
IV. Matheson I, Kristensen K, Lunde PKM. Drug utilization in breast-feeding women. A survey in Oslo. Eur J Clin Pharmacol 1990; 38: 453-9.
V. Matheson I, Bredesen JE, Lunde PKM. Midazolam and nitrazepam in the maternity ward. Milk concentrations and hypnotic effects. Br J Clin Pharmacol, 1990; 30: 787-93.
VI. Matheson I, Sande HA, Gaillot J. The excretion of zopiclone into breast milk. Br J Clin Pharmacol, 1990; 30: 267-71.
VII. Matheson I, Samseth M, Løberg R, Fægri A, Prentice A. Milk transfer of phenoxymethyl-penicillin during puerperal mastitis. Br J Clin Pharmacol 1988; 25: 33-40.
VIII. Nielsen ST, Matheson I, Nepper-Rasmussen J, Skinnemoen K, Andrew E, Hafsahl G. Excretion of iohexol and metrizoate in human breast milk. Acta Radiol 1987; 28: 523-6.

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